313

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SOME CONDITIONS CONTROLLING INTERNAL SECRETION *

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No one may now question the great influence of the glands of internal secretion on important physiologic processes. The growth of the body, the proper development of the nervous system, the appearance of secondary sex characters, the orderly sequences in the reproductive cycle, the nature and rate of chemical changes in the body—all these fundamental processes seem to be in the grip of the endocrine organs. Agents which can determine whether an individual shall be a giant or a dwarf, an idiot or a normally intelligent person, a "sissy" or a real male, a bearded lady or a woman; agents which are essential to normal metabolism—indeed, whose destruction may lead promptly to death—must evidently be respected.

There appears to be a tendency just now, however, to pay these glands not only respect, but reverence and homage and a blind worship. The endocrine organs are referred to as "regulators of metabolism" and as "regulators of personality," as if they occupied an imperious position in our internal economy, and the other organs were mere servants to do their bidding. This is a concept which is largely based, I believe, on the marked effects of either the destruction of endocrine glands or the development of tumors and other pathologic states within them. When a gland is destroyed it is gone forever, and its absence tells us nothing about how it worked or the modulations of activity it may have had. On the other hand, tumors *are* dictators in relation to the rest of the body, living riotously outside the law.

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Thus, two extreme conditions, neither of them normal nor even remotely physiologic, have led to the assumption of an endocrine almightiness. Is that the mode of organization of the body? Is our internal government autocratically ruled by a czar or a kaiser or by groups of kings and princes, represented by the ductless glands, or is there a more democratic arrangement whereby influences pass to and fro among the various parts of the organization and, after many mutual adjustments, finally express themselves in function?

The physiologist regards the body in the latter sense —as a system of organs, each performing its service, each influenced by other organs and capable in turn of influencing other organs, and each having a use and a value only in relation to the others.

Questions now arise regarding the real status of the glands of internal secretion. If they have not the dominant position commonly assumed for them, how may they be subordinated? What influences can be brought to bear on them in such a way as to modify their activity? These are important questions to have answered—important because of the profound effects which the ductless glands themselves are capable of exerting. In a brief survey I propose to present some of the evidence for physiologic control of the internal secretions.

EVIDENCE FOR NERVOUS CONTROL

We now have evidence that at least the suprarenal medulla, the liver and the thyroid gland are subject to sympathetic nerve impulses. Stimulation of the splanchnic nerves causes a discharge of epinephrin from the suprarenal glands into the blood stream in an amount which markedly affects other organs. Such stimulation also liberates sugar from the liver. Uridil and I [1] have shown that under stimulation the liver yields another substance which raises blood pressure and causes an acceleration of the denervated heart. Furthermore, Smith and I [2] recently described experiments that confirm earlier work and testify to the efficacy of cervical sympathetic stimulation in calling forth a secretion from the thyroid gland.

1. Cannon, W. B., and Uridil, J. E.: Am. J. Physiol. **58**: 353 (Dec.) 1921.

2. Cannon and Smith: Am. J. Physiol. **60**: 476, 1922.

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It is well known that the sympathetic division of the autonomic system is brought into action by pain, asphyxia and great emotional excitement. That the three endocrine organs mentioned above may be strongly influenced by such conditions has been proved by numerous observations made both on experimental animals and in clinical cases. Extra epinephrin circulating in the blood when a sensory nerve is stimulated or signs of rage are evoked can be demonstrated by a faster beat of the denervated heart.[3] Emotional hyperglycemia or glycosuria, due doubtless to extra sugar freed from the liver, has been observed in cats disturbed by barking dogs, in students undergoing severe examination,[4] in aviators,[5] and in citizens terrorized by bombardments and air raids.[6] The thyroid likewise may be stimulated by painful and asphyxial conditions. Smith and I were able to obtain quite as striking results by such stimuli as we obtained by direct excitation of the cervical sympathetic strand. The considerable number of cases of exophthalmic goiter reported as occurring in consequence of stressful circumstances during the war [7] may perhaps be taken as additional indication of an influence on the thyroid gland exercised by the sympathetic nervous system.

Another gland which may be affected by nerve impulses is the posterior lobe of the pituitary. Weed, Cushing and Jacobson [8] have reported that stimulation of the superior cervical sympathetic ganglion induces glycosuria (even though all nervous connections with the abdominal viscera have been severed), and that the result fails to occur if the posterior lobe of the pituitary has previously been removed. In harmony with this result is Shamoff's testimony that the same stimulation induces, besides glycosuria, such diuresis as is induced by pituitary extract.[9] The inference that a hormone is discharged from the pituitary as a result of stimulation has been somewhat invalidated by Rabens and Lifschitz,[10] who were unable to produce glycosuria by stimulating under physiologic conditions or to modify

3. Cannon, W. B.: Am. J. Physiol. **50**: 399 (Dec.) 1919.
4. Folin, Denis and Smillie: J. Biol. Chem. **17**: 519, 1914.
5. Marañon, G.: Siglo. méd. **66**: 573 (July 19) 1919.
6. Etienne and Richard: Revue méd., Oct. 12, 1918.
7. Marañon, G.: Ann. de méd. **9**: 81 (Feb.) 1921.
8. Weed, Cushing and Jacobson: Bull. Johns Hopkins Hosp. **24**: 40, 1913.
9. Shamoff, V. N.: Am. J. Physiol. **39**: 279 (Jan.) 1916.
10. Rabens and Lifschitz: Am. J. Physiol. **36**: 47, 1914.

the glycosuria due to ether. Furthermore, though Keeton and Becht [11] did augment the reducing substance in the blood by direct excitation of the pituitary, the effect was abolished by severance of the splanchnic nerves. A nervous control of secretion from the posterior lobe of the pituitary is therefore in question.

Thus far, attempts to prove that internal secretion of the pancreas is subject to sympathetic impulses have proved futile. Allen [12] has testified to his inability to secure any indication of such nervous control, and von Noorden [13] has declared that he has not seen any influence of the excitements of war in producing true diabetes. Indeed, in the Central Empires, where the food shortage was marked, the deaths from diabetes were fewer toward the end of the war, despite the increasing nervous stress, than they had been at the beginning.[14] According to de Corral,[15] however, stimulation of vagus fibers below the branches to the heart results in a reduction of the sugar content of the blood. This research, not yet confirmed, offers the only hint of which I am aware that the islet cells may be governed by nerves.

Nervous control of ductless glands involves the idea that they, like other structures governed by nerves, have their activities adapted to the needs of the body at different times. That the organism survives and lives normally when nerves to the suprarenal [16] or thyroid [17] gland are severed is not proof that the nerves are useless, any more than the continued service of the denervated heart as a pump is proof that the vagus and accelerator nerves are useless. The nerves may have, in relation to the glands, just as in relation to the heart, a tonic action for routine purposes; and at times of critical need they may have a special, or what I have called an "emergency" function, capable of rapidly mobilizing the bodily forces, internal secretions included, for the welfare of the organism as a whole.

No better illustration could be given of the tendency to regard the internal secretions as supreme and the

11. Keeton and Becht: Am. J. Physiol. **39**: 109, 1915.
12. Allen, F. M.: J. Metabol. Res. **1**: 53 (Jan.) 1922.
13. Von Noorden, C.: Med. Klin. **12**: 991 (Sept.) 1916.
14. Magnus-Levy: Deutsch. med. Wchnschr. **56**: 1150, 1919.
15. De Corral: Ztschr. f. Biol. **58**: 395, 1918.
16. Stewart, G. N., and Rogoff, J. M.: J. Pharmacol. & Exper. Therap. **10**: 1 (July) 1917.
17. Manley and Marine: Proc. Soc. Exper. Biol. & Med. **12**: 202, 1915.

nervous system as quite subordinate than in the theory underlying the clinical conceptions of vagotonia and sympathicotonia. Indeed, Eppinger and Hess,[18] the authors of the theory, have concluded that "the entire vegetative nervous system is under the control of the glands of internal secretion." Epinephrin is, indeed, able to reproduce almost all the changes that occur when sympathetic impulses are discharged. It has been supposed, therefore, to exercise a tonic action on sympathetic endings. For example, the height of arterial pressure is assumed to depend on the constant discharge of epinephrin into the blood stream, and a low blood pressure is ascribed to "hypo-adrenia." In order to have an antagonist for epinephrin—some substance which would take command of the opposing forces—Eppinger and Hess have conjured up a hypothetic hormone, "autonomin," acting like pilocarpin and physostigmin on the nerve endings of the cranial division of the automatic system. This assumed entity, first predicated in 1910, has never had the fortune of a real existence. Nevertheless, clinical literature has been rife with descriptions of cases with vagotonic and sympathicotonic dispositions.

It is well to recognize that there is no good evidence that epinephrin has any tonic effect in maintaining blood pressure. Aub [19] has measured the pressure four or five days after removal of both suprarenal glands and found it normal. Since epinephrin disappears from the blood a few minutes after it is injected or secreted, the continued normal pressure cannot be due to persistence of that substance in the blood. Stewart and Rogoff [16] have severed the nerves to one suprarenal gland and removed the other. Practically no demonstrable amount of epinephrin is secreted under such circumstances, and yet the animals remained for months in quite good condition. Gley and Quinquaud [20] have shown that vascular reflexes occur fully as effectively with the suprarenal glands absent as they do when the glands are present. Furthermore, Hoskins and McClure [21] pointed out, years ago, that an amount of

18. Eppinger and Hess: Vagotonia, English translation, New York, 1915, p. 9.

19. Aub: Am. J. Physiol., to be published.

20. Gley and Quinquaud: J. de physiol. et de path. gén. **17**: 807, 1918.

21. Hoskins, R. G., and McClure, C. W.: The Adrenal Glands and Blood Pressure, Arch. Int. Med. **10**: 343 (Oct.) 1912.

epinephrin required to cause a rise of blood pressure is sufficient to stop all motions of the stomach and intestine. A ridiculous mechanism it would be that would stop digestion in order to provide a few extra millimeters of arterial tension! There is no satisfactory evidence that, in natural quiet existence, the suprarenal medulla gives off any secretion whatever. In times of stress it is brought into action by nerve impulses and may, indeed, then support the influence of the sympathetic system, and have besides special functions of its own.[22]

The general arrangement of the sympathetic division is favorable to diffuse and widespread action in which a distributed chemical agent could participate. The vagus endings and the endings of the other parts of the cranial autonomic division lie in or near the organs innervated, and are therefore favorable to separate and discriminating action. By means of the general diffuse action of the sympathetic, and the opposite particular action of the parts of the cranial autonomic supply, every variety of change is provided for. All the viscera can be affected simultaneously in one way or the other through increased or decreased tone of the sympathetic division. And any special organ can be separately affected one way or the other through increased or decreased tone in the special nerve of the opposed cranial division that is supplied directly to the organ. The sympathetic is like the soft and loud pedals, modulating all the notes together; the cranial autonomic is like the separate keys.

A dilated pupil, for example, due to increased sympathetic activity attending excitement, should be accompanied by a rapid heart rate, vasoconstriction, stoppage of the motions of the stomach and intestine, and other evidences of widespread sympathetic influences. Epinephrin secreted at the same time would act synergistically with the nerve impulses. On the other hand, constriction of the iris by action of the motor oculi when the light is strong may not be accompanied by disturbance of any other part of the cranial autonomic supply to the viscera. Indeed, there is no conceivable advantage in having a mechanism in which strong light would result not only in a smaller pupil,

22. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, 1915, p. 184.

but also in a slower heart rate and an increased tone of the gastro-intestinal tract. As one can readily perceive, a single substance, "autonomin," acting extensively, like pilocarpin, on cranial autonomic endings, might have most disorderly effects in forcing to operate coincidently and in an unadapted manner organs whose functions in calm existence are not importantly related to one another.

The ill-based theory of vagotonia has almost no respectable evidence to support it. Not only the criticism of laboratory workers but also the testimony of clinical observers has done much to discredit it. Cases are cited in which patients are equally hypersensitive to epinephrin and pilocarpin,[23] in which pilocarpin, atropin and epinephrin produce practically identical effects on the blood,[24] in which both atropin and epinephrin will stop auricular fibrillation,[25] and in which careful studies on various bodily functions showed no consistent sensitization to either the "sympathicotonic" or the "vagotonic" drugs. In the presence of the foregoing evidence, "vagotonia" becomes merely a name—a name which, as applied to the entire cranial autonomic division and presupposing a general reinforcing and vagotonic hormone, is wholly without meaning.

Reference was made above to the fact that activity of the sympathetic system may be varied up or down. Strong stimulation of an afferent nerve will cause vasoconstriction and other indications of diffuse sympathetic discharge, including suprarenal secretion. On the other hand, stimulation of the central end of the depressor nerve will cause vasodilation and a checking of any suprarenal secretion which may be going on.[26] Quite possibly, therefore, conditions may exist in the body, characterized by either greater or less sympathetic tone than normal; but such states would not be determined by independent dominance of suprarenal secretion, for, as shown above, lack of any secretion at all does not lessen the efficacy of sympathetic impulses, and extra secretion is ordinarily dependent on the effect of nerve impulses. The condition of the nervous sys-

23. Lehmann: Berl. klin. Wchnschr. **56**: 772, 1919.
24. Friedbery: Deutsch. med. Wchnschr. **46**: 480, 1920.
25. Loeffler: Schweiz Arch. f. Neurol. u. Psychiat. **8**: 177, 1921.
26. Cannon, W. B., and Rapport, D.: Am. J. Physiol. **58**: 338 (Dec.) 1921.

tem, not of the suprarenal medulla, therefore, is of primary moment.

In the foregoing review, evidence has been adduced to show the subjection of certain endocrine glands to nervous government. This emphasis, however, should not be interpreted as implying an independent dominance of the nervous system, for it, like other systems, is conditioned in its activities. Again I wish to lay stress on the fact that the body is an organism, and that the parts collaborate and exercise mutual influences on one another.

EVIDENCE FOR HUMORAL CONTROL

Nerves have been described as present in other of the endocrine glands than those mentioned above—for example, in the anterior lobe of the pituitary body [27] and in the parathyroid bodies.[28] On the other hand, it is reported that no nerve fibers are distributed to the interstitial cells of the testis, and very few to the suprarenal cortex. Nevertheless, both these structures may undergo hyperplasia, associated, at least in the case of the interstitial tissue, with seasonal depression at times of sex activity.[29] Evidently some other mode of control besides nerve impulses must prevail in such conditions. And since the blood stream alone brings the glands into relation with other parts, it is naturally assumed that the influences affecting the glands and passing away from them are conveyed in the circulating blood. In other words, the influences are of the humoral type.

The presence of a nervous control of internal secretion does not preclude a humoral control. Thus, the heart and the stomach and intestine are readily influenced by nerve impulses. But they are likewise affected by epinephrin discharged by the suprarenals, i. e., by a humoral agent. Also the thyroid, though subject to nerve stimulation, is responsive to chemical factors brought by the blood. For example, Cattell and I [30] found some years ago that stimulation of a discharge from the suprarenal medulla would cause an electrical action current in the thyroid.

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27. Berkeley: Brain **17**: 515, 1894.
28. Schäfer: The Endocrine Organs, London, 1916, p. 21.
29. Tandler and Grosz: Arch. f. Entwicklungsm. **33**: 297, 1911.
30. Cannon, W. B., and Cattell, M.: Am. J. Physiol. **41**: 74 (July) 1916.

When we begin to consider the evidence for interrelation of the ductless glands, we find ourselves in a maze of complex possibilities, contradictory reports and uncertain inferences. Much of the evidence is derived from distant effects of ablation or destruction of one or more of the glands, or from changes due to tumor growth, or to feeding gland substance. None of these circumstances can be regarded as physiologic. The results may be suggestive of *some* relation between the gland removed, or abnormal, or fed, and the other gland or glands which are altered thereby. But it is hazardous to draw inferences from pathologic states relative to physiologic processes. And even if there is *some* relation, we have not made satisfactory progress until we know what the relation is, the way it works and its full significance. If we knew nothing of the function of the heart and as much as we now know about the endocrine organs, we might be led to infer that the semilunar valves exercise an inhibitory influence on the growth of the heart; for does not destruction or injury of the valves result in an enlargement of that organ? Do we reason any better than this in many of our inferences from the effects of experimental removal of the endocrine organs? We know almost nothing, for example, about the normal functioning of the suprarenal cortex. Several observers have confirmed Hoskins'[31] observation that feeding thyroid gland enlarges the suprarenal body, especially the cortical portion, according to Herring.[32] It is reported to be enlarged also by starvation[33] or by a diet deficient in vitamins.[34] And Gley[35] and also Carlson[36] have found enlargement of the suprarenal bodies after removing the thyroid glands. Is the enlargement due to stimulation by the thyroid, or is it compensatory to increased metabolism, or is it a biologic response conservative of important bodily material when the supply is low or is being rapidly consumed? These are some of the possibilities. Certainly, in the presence of these complexities one has no clear idea of thyroid influence on suprarenal function.

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31. Hoskins: Am. J. Physiol. **26**: 426, 1910.
32. Herring: Quart. J. Exper. Physiol. **11**: 47, 231, 1917.
33. Byrne, C. H. C.: Brit. M. Jour. **2**: 135 (Aug. 2) 1919.
34. McCarrison, R.: Brit. M. J. **2**: 236 (Aug. 14) 1920.
35. Gley: Arch. internat. de physiol. **14**: 175, 1914.
36. Carlson, A. J., in discussing Cannon, W. B.: Results of Recent Studies on Ductless Glands, J. A. M. A. **67**: 1483 (Nov. 18) 1916.

Possibly too much emphasis has been laid on mere changes of size. More than thirty years ago, Rogowitsch [37] first noted that thyroidectomy is followed by hypertrophy of the pituitary body. This observation has been confirmed by numerous investigators. Kamo,[38] who removed the thyroid from young dogs, found, after a few months, marked pituitary enlargement, even to more than twice the normal size, manifested chiefly in the anterior lobe. We commonly associate hypertrophy with extra activity, and we have evidence that extra activity of the anterior lobe of the pituitary body is attended by an overgrowth of the skeleton. Animals deprived of the thyroid, however, are stunted in growth. Here we have an instance of hypertrophic change in one gland induced by removal of another, but with no corresponding hyperfunctional effect.

Perhaps we shall have clearer signs of the cooperation of the endocrine organs if we consider briefly the influence of various representative glands on a common function. For illustrative purposes I propose to call attention to some of the effects of the glands on certain bodily processes, which were mentioned earlier —growth, reproduction and metabolism.

The relation between overgrowth of the skeleton, as in gigantism and acromegaly, and hyperplasia of the anterior lobe of the pituitary, is now fairly well established. Extra skeletal growth is also associated with early castration. On the other hand, both clinical and experimental studies point to early pituitary deficiency as causing failure of bony development. This form of dwarfism is characterized by both short and slender bones. A third gland whose function is essential to growth is the thyroid, for in its absence the stature is stunted. Here are three endocrine organs, all having marked influence on the attainment of normal size. One could readily speculate as to how they influence one another—the pituitary and thyroid appearing to work cooperatively and the gonads acting as a check on them—but we need facts rather than speculation.

Reproduction depends on the gonads, of course, but it also depends on the thyroid and the pituitary glands. If the young animal is deprived of either the thyroid

37. Rogowitsch: Beitr. z. path. Anat. u. z. allg. Path. **4**, 1889.
38. Kamo: Jap. Med. Lit. **3**: 33, 1918.

or the pituitary, the generative organs are only slowly or imperfectly developed, so that a condition of sexual infantilism persists. Hyperplasia of the pituitary, and also of the suprarenal cortex, in the young, is sometimes associated with precocious sexual maturity and activity. Both the thyroid and the suprarenal cortex become enlarged during pregnancy. Thus, the evidence seems to point to the thyroid and the pituitary glands and to the suprarenal cortex as factors essential to proper establishment of the reproductive function, and also possibly collaborating, in the female, in the performance of that function.

The pancreas, the suprarenals and the liver primarily, and likewise the thyroid and the pituitary, are all concerned with carbohydrate metabolism. As is well known, excision of the pancreas results in diabetes, stimulation of the liver or injection of epinephrin increases the sugar in the blood, and removal of either the thyroid or the pituitary raises the assimilation limit of sugar. Diabetes is occasionally associated with acromegaly and with exophthalmic goiter. Probably all five of the glands mentioned above either cooperate or form a fairly stable combination of opposed influences. But, again, how these organs are interrelated in their effects on metabolic processes is not at all clear.

In the foregoing paragraphs I have merely hinted at some of the signs of cooperation among certain endocrine glands. My purpose in doing so was to make the point that here, just as in the nervous government of internal secretion, there are indications that we are dealing with arrangements which are normally well ordered and subject to automatic control. Bodily functions are managed by a system of checks and balances—by mutual adjustments such as those between antagonistic muscles, and by maintained equilibria, such as those between material income and outgo, and between acid and base in the blood. We are justified by what we already know of bodily organization in looking for similar modes of restraining and releasing the internal secretions. If the endocrine glands are regarded as the regulators of important physiologic processes, normally they are well regulated regulators. Much work must still be done, however, before we shall know the mechanisms whereby the control of these agents is exercised. But the work is

highly important because of the potency of the endocrine organs when they are deficient or when they escape control and through pathologic activity play havoc with our internal adjustments.

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